A multi-physics oxygenation model:
from biological derivation to the numerical simulation of real-life scenarios

Laurea Magistrale in Mathematical Engineering - Ingegneria Matematica

Politecnico di Milano

A. Y. 2021-22

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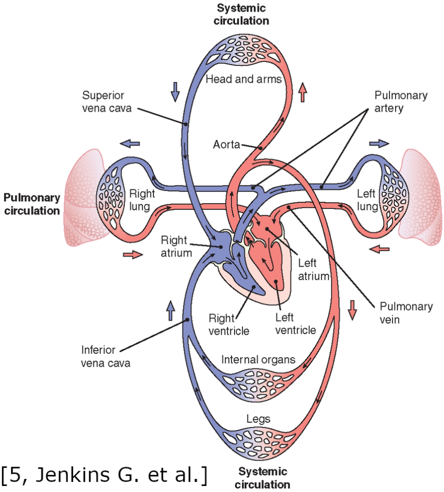
Motivations

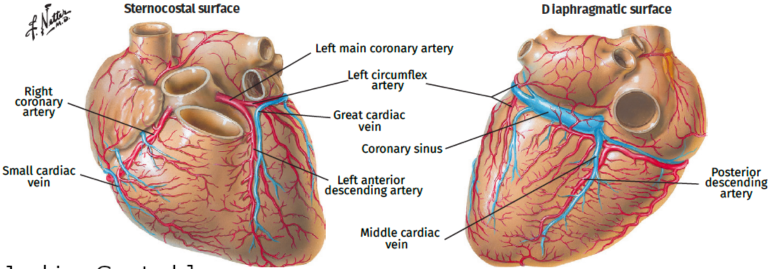
- The cardiovascular diseases are one of the major causes of death worldwide
- Mathematical models and numerical simulations could help in the understanding of cardiovascular diseases
- The myocardium needs a continuous oxygen supply to work properly

Motivations



[5, Jenkins G. et al.]

Motivations



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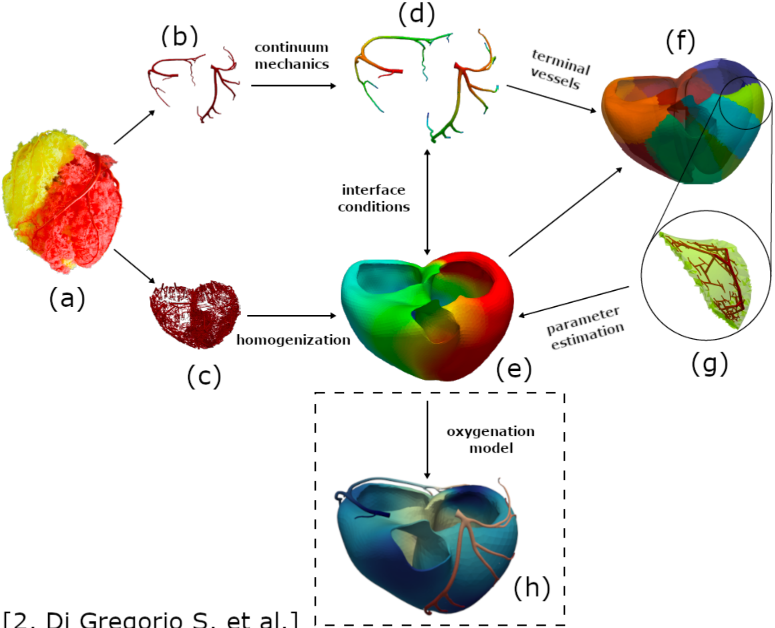
Design of multi-physics model



[2, Di Gregorio S. et al.]

Oxygen exchange in microvasculature

Oxygenation model unknown scalar fields

Variable	Measure unit	Description
PO_2^3	$[\mathrm{mmHg}]$	O_2 partial pressure
SO_2^3	$[-]$	O_2 saturation
PO_2^m	$[\mathrm{mmHg}]$	O_2 partial pressure in muscle

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Oxygen fluxes

- delivered from the capillaries to the myocardium

$$\lambda_{O_2}^{\mathrm{del}}(t) = \frac{1}{|\Omega_M|} \int_{\Omega_M} \widetilde{P}\alpha^{-1}(PO_2^3 - PO_2^m)\, d\boldsymbol{x} \qquad \Lambda_{O_2}^{\mathrm{del}}(t) = \int_0^t \lambda_{O_2}^{\mathrm{del}}(u)\, du$$

- consumed by the myocardium to produce ATP

$$\lambda_{O_2}^{\mathrm{cons}}(t) = \frac{1}{|\Omega_M|} \int_{\Omega_M} \psi_m \widetilde{\xi}_0 \alpha^{-1} \left(1 + \frac{PO_2^{m,50}}{PO_2^m}\right)^{-1} d\boldsymbol{x} \qquad \Lambda_{O_2}^{\mathrm{cons}}(t) = \int_0^t \lambda_{O_2}^{\mathrm{cons}}(u)\, du$$

Oxygen exchange in microvasculature - complete model

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\begin{cases}
\frac{\partial}{\partial t} PO_2^3 + \psi_3^{-1} \nabla \cdot \left(PO_2^3 \boldsymbol{u}_3 \right) + \mu \Delta PO_2^3 = n \alpha [Hb*] k_- \left(SO_2^3 - (1 - SO_2^3) \left(\frac{PO_2^3}{PO_2^{50}} \right)^n \right) \\
\qquad + \psi_3^{-1} \widehat{\phi}_{2,3} PO_2^a - \psi_3^{-1} \widehat{\phi}_{3,v} PO_2^3 - \psi_3^{-1} \widetilde{P} (PO_2^3 - PO_2^m) \\
\frac{\partial}{\partial t} SO_2^3 + \psi_3^{-1} \nabla \cdot \left(SO_2^3 \boldsymbol{u}_3 \right) + \mu \Delta SO_2^3 = - k_- \left(SO_2^3 - (1 - SO_2^3) \left(\frac{PO_2^3}{PO_2^{50}} \right)^n \right) + \psi_3^{-1} \widehat{\phi}_{2,3} SO_2^a - \psi_3^{-1} \widehat{\phi}_{3,v} SO_2^3 \\
\frac{\partial}{\partial t} PO_2^m = \psi_m^{-1} \widetilde{P} (PO_2^3 - PO_2^m) - \widetilde{\xi}_0 \left(1 + \frac{PO_2^{m,50}}{PO_2^m} \right)^{-1}
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Oxygen exchange in microvasculature - reduced model

Reduced oxygenation model unknown scalar fields

Assuming that the chemical reaction are in equilibrium, we get

$$[O_2*]^3 := n[Hb*]\, SO_2^3 + \alpha^{-1}\, PO_2^3 =: g(PO_2^3), \quad SO_2 = \left(1 + \left(\frac{PO_2^{50}}{PO_2^3}\right)^n\right)^{-1}$$

Variable	Measure unit	Description
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Multi-physics three-compartments oxygenation model

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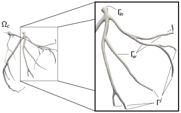

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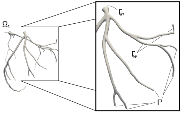

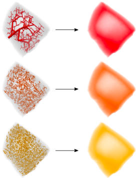

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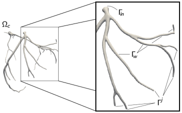

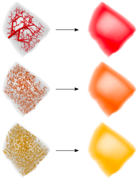

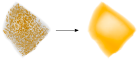

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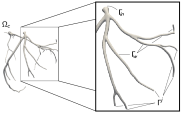
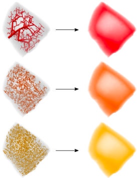
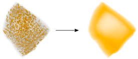


Navier-Stokes

$$
\begin{cases}
\rho\left(\dfrac{\partial \boldsymbol{u}_C}{\partial t} + (\boldsymbol{u}_C \cdot \nabla)\,\boldsymbol{u}_C\right) - \mu_C \nabla \cdot \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) + \nabla p_C = \boldsymbol{0} & \text{in } \Omega_C \\
\nabla \cdot \boldsymbol{u}_C = 0 & \text{in } \Omega_C \\
p_C - \mu_C \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) \boldsymbol{n} \cdot \boldsymbol{n} - \dfrac{1}{\alpha^j} \displaystyle\int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma = \dfrac{1}{\left|\Omega_M^j\right|} \displaystyle\int_{\Omega_M^j} p_1 \, d\boldsymbol{x} & \text{on } \Gamma^j
\end{cases}
$$





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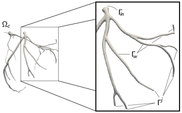
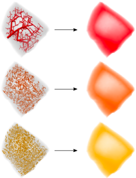


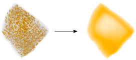
Navier-Stokes

$$\begin{cases} \rho\left(\dfrac{\partial \boldsymbol{u}_C}{\partial t} + (\boldsymbol{u}_C \cdot \nabla)\,\boldsymbol{u}_C\right) - \mu_C \nabla \cdot \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) + \nabla p_C = \boldsymbol{0} & \text{in } \Omega_C \\ \nabla \cdot \boldsymbol{u}_C = 0 & \text{in } \Omega_C \\ p_C - \mu_C \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) \boldsymbol{n} \cdot \boldsymbol{n} - \dfrac{1}{\alpha^j} \displaystyle\int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma = \dfrac{1}{\left|\Omega_M^j\right|} \displaystyle\int_{\Omega_M^j} p_1 \, dx & \text{on } \Gamma^j \end{cases}$$



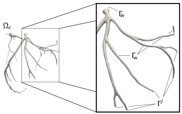
Darcy

$$\begin{cases} \boldsymbol{u}_1 + \boldsymbol{K}_1 \nabla p_1 = \boldsymbol{0}, \quad \boldsymbol{u}_2 + \boldsymbol{K}_2 \nabla p_2 = \boldsymbol{0}, \quad \boldsymbol{u}_3 + \boldsymbol{K}_3 \nabla p_3 = \boldsymbol{0} & \text{in } \Omega_M \\ \nabla \cdot \boldsymbol{u}_1 = \displaystyle\sum_{j=1}^{J} \dfrac{\chi_{\Omega_M^j}}{\left|\Omega_M^j\right|} \displaystyle\int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma - \beta_{1,2}\,(p_1 - p_2) & \text{in } \Omega_M \\ \nabla \cdot \boldsymbol{u}_2 = -\beta_{2,1}\,(p_2 - p_1) - \beta_{2,3}\,(p_2 - p_3) & \text{in } \Omega_M \\ \nabla \cdot \boldsymbol{u}_3 = -\beta_{3,2}\,(p_3 - p_2) - \gamma\,(p_3 - p_v) & \text{in } \Omega_M \end{cases}$$



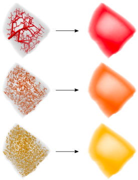
Multi-physics three-compartments oxygenation model

[2, Di Gregorio S. et al.]



Navier-Stokes

$$\begin{cases} \rho \left(\dfrac{\partial \boldsymbol{u}_C}{\partial t} + (\boldsymbol{u}_C \cdot \nabla)\, \boldsymbol{u}_C \right) - \mu_C \nabla \cdot \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T \right) + \nabla p_C = \boldsymbol{0} & \text{in } \Omega_C \\ \nabla \cdot \boldsymbol{u}_C = 0 & \text{in } \Omega_C \\ p_C - \mu_C \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T \right) \boldsymbol{n} \cdot \boldsymbol{n} - \dfrac{1}{\alpha^j} \boxed{\displaystyle\int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma} = \dfrac{1}{\left|\Omega_M^j\right|} \displaystyle\int_{\Omega_M^j} \boxed{p_1}\, d\boldsymbol{x} & \text{on } \Gamma^j \end{cases}$$



Darcy

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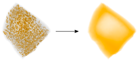
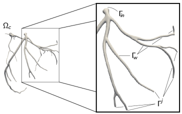
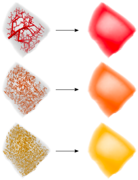
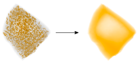


Multi-physics three-compartments oxygenation model

[2, Di Gregorio S. et al.]







Navier-Stokes

$$
\begin{cases}
\rho\left(\dfrac{\partial \boldsymbol{u}_C}{\partial t} + (\boldsymbol{u}_C \cdot \nabla)\,\boldsymbol{u}_C\right) - \mu_C \nabla \cdot \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) + \nabla p_C = \boldsymbol{0} & \text{in } \Omega_C \\
\nabla \cdot \boldsymbol{u}_C = 0 & \text{in } \Omega_C \\
p_C - \mu_C \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) \boldsymbol{n} \cdot \boldsymbol{n} - \dfrac{1}{\alpha^j} \displaystyle\int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma = \dfrac{1}{\left|\Omega_M^j\right|} \int_{\Omega_M^j} p_1 \; dx & \text{on } \Gamma^j
\end{cases}
$$

Darcy

$$
\begin{cases}
\boldsymbol{u}_1 + \boldsymbol{K}_1 \nabla p_1 = \boldsymbol{0}, \qquad \boldsymbol{u}_2 + \boldsymbol{K}_2 \nabla p_2 = \boldsymbol{0}, \qquad \boldsymbol{u}_3 + \boldsymbol{K}_3 \nabla p_3 = \boldsymbol{0} & \text{in } \Omega_M \\
\nabla \cdot \boldsymbol{u}_1 = \displaystyle\sum_{j=1}^{J} \dfrac{\chi_{\Omega_M^j}}{\left|\Omega_M^j\right|} \int_{\Gamma^j} \boldsymbol{u}_C \cdot \boldsymbol{n}\, d\gamma - \beta_{1,2}\,(p_1 - p_2) & \text{in } \Omega_M \\
\nabla \cdot \boldsymbol{u}_2 = -\beta_{2,1}\,(p_2 - p_1) - \beta_{2,3}\,(p_2 - p_3) & \text{in } \Omega_M \\
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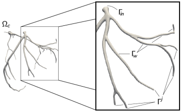
\end{cases}
$$

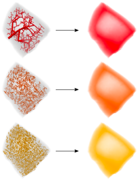
Oxygenation

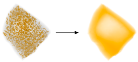
$$
\begin{cases}
\dfrac{\partial}{\partial t}[O_2*]^3 + \psi_3^{-1} \nabla \cdot \left(-\boldsymbol{K}_3 \nabla p_3 \; [O_2*]^3\right) + \mu \Delta [O_2*]^3 = \\
\quad \psi_3^{-1} \; \beta_{3,2}\,(p_3 - p_2) \; [O_2*]^2 - \psi_3^{-1} \; \gamma\,(p_3 - p_v) \; [O_2*]^3 \\
\quad -\psi_3^{-1} \widetilde{P} \alpha^{-1} \left(g^{-1}([O_2*]^3) - PO_2^m\right) & \text{in } \Omega_M \\
\dfrac{\partial}{\partial t} PO_2^m = \psi_m^{-1} \widetilde{P} (g^{-1}([O_2*]^3) - PO_2^m) - \widetilde{\xi}_0 \left(1 + \dfrac{PO_2^{m,50}}{PO_2^m}\right)^{-1} & \text{in } \Omega_M
\end{cases}
$$

Multi-physics three-compartments oxygenation model

[2, Di Gregorio S. et al.]







Navier-Stokes

$$
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\end{cases}
$$

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$$

Oxygenation

$$
\begin{cases}
\dfrac{\partial}{\partial t}[\mathrm{O}_2*]^3 + \psi_3^{-1}\nabla\cdot\left(-\boxed{\boldsymbol{K}_3\nabla p_3}[\mathrm{O}_2*]^3\right) + \mu\Delta[\mathrm{O}_2*]^3 = \\
\psi_3^{-1}\boxed{\beta_{3,2}\,(p_3 - p_2)}[\mathrm{O}_2*]^2 - \psi_3^{-1}\boxed{\gamma\,(p_3 - p_v)}[\mathrm{O}_2*]^3 \\
-\psi_3^{-1}\widetilde{P}\alpha^{-1}\left(g^{-1}([\mathrm{O}_2*]^3) - \mathrm{PO}_2^m\right) & \text{in } \Omega_M \\
\dfrac{\partial}{\partial t}\mathrm{PO}_2^m = \psi_m^{-1}\widetilde{P}(g^{-1}([\mathrm{O}_2*]^3) - \mathrm{PO}_2^m) - \widetilde{\xi}_0\left(1 + \dfrac{\mathrm{PO}_2^{m,50}}{\mathrm{PO}_2^m}\right)^{-1} & \text{in } \Omega_M
\end{cases}
$$

Numerical discretization

- Solver implemented inside **life^{x}** high-performance library for cardiac applications (C++), within the **iHEART** project
- We leveraged on preexisting implementation of fluid dynamics and perfusion subproblems, implementing the oxygenation one and the coupling conditions
- Regarding fluid dynamics and perfusion subproblems, we used
  - FEM P1-P1 with elements and SUPG-PSPG stabilization for space discretization
  - semi-implicit Euler scheme for time discretization

Numerical discretization

- Regarding the **oxygenation** model, we used
  - **functional space** $L^2\left([0,T], H^1(\Omega_M)\right)$ for $[O_2*]$ and PO_2^m
  - **FEM** with P1-P1 elements for space discretization
  - **semi-implicit** Euler schema for time discretization

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$$\begin{bmatrix} \mathbb{A}^k & \mathbb{O} \\ \mathbb{O} & \mathbb{I} \end{bmatrix} \begin{bmatrix} [O_{\mathbf{2}}*]^{3,k+1} \\ PO_{\mathbf{2}}^{m,k+1} \end{bmatrix} = \begin{bmatrix} \boldsymbol{F}^k \\ \boldsymbol{G}^k \end{bmatrix}$$

Tests on idealized geometries

We performed many tests to check the model validity and its implementation in life^x. We made comparisons between

- **complete** and **reduced** model to check the validity of the quasistatic-chemistry assumption

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Tests on idealized geometries

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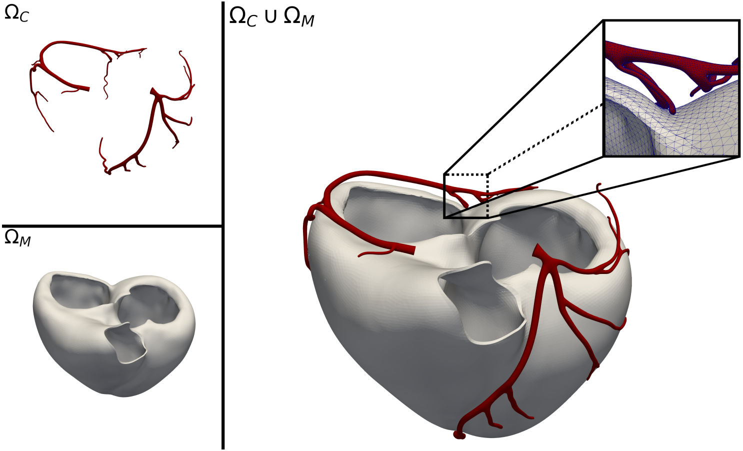
We made comparisons between

- **complete** and **reduced** model to check the validity of the quasistatic-chemistry assumption
- **3D** and **0D** models to check if, in proper conditions, the 0D model is a good approximation of the 3D one
- **semi-coupled** model (only perfusion coupling) and **uncoupled**, to test the coupling condition
- **coupled** model (perfusion and coronaries) and **semi-coupled**, to test both the coupling conditions

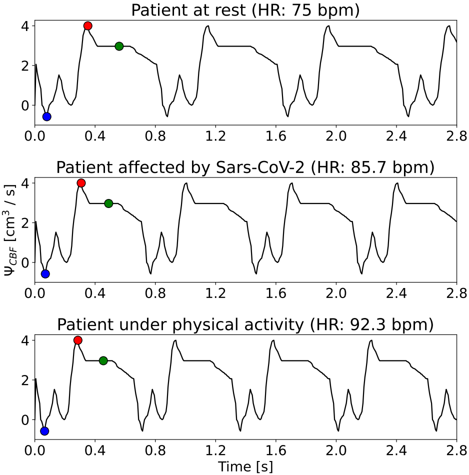
Real geometries

- 3D Human Heart Model provided by Zygote [URL: `https://www.zygote.com/`]
- $146,673$ nodes for Ω_C and $267,374$ nodes for Ω_M
- Simulations on 56 cores running Intel Xeon Gold 6238@2.10 GHz, using the computational resources available at MOX, Dipartimento di Matematica



Real-life scenarios

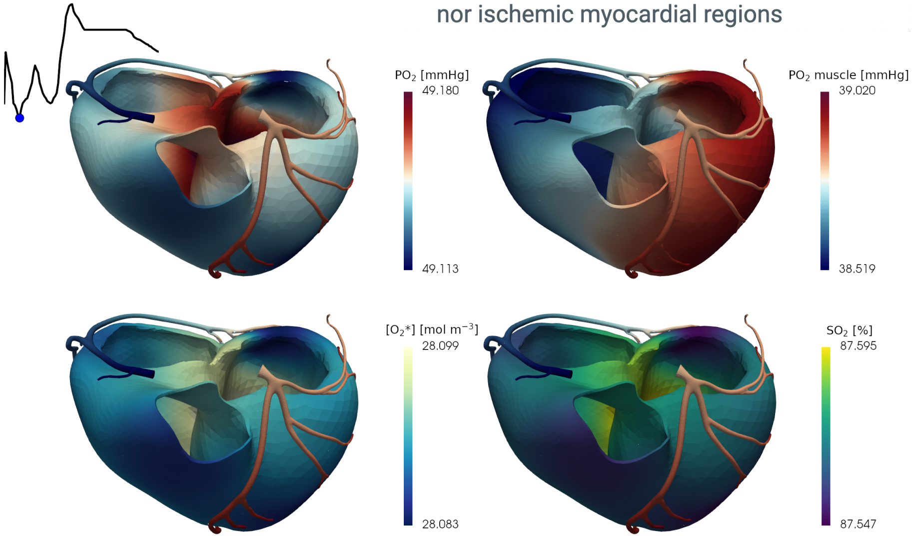
- **Physiological scenario** and comparison between simulations on **real** and **idealized** geometries
- Effects of **physical activity** on a healthy subject
- Effects of **SARS-CoV-2** infection
- Effects of **physical activity** on a patient with **SARS-CoV-2** infection



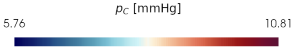
Scenario	Period	HR	Color		
			Blue	Red	Green
Pt. at rest	0.8 s	75 beat min^{-1}	0.08 s	0.352 s	0.560 s
Pt. with SARS-CoV-2	0.7 s	85.7 beat min^{-1}	0.070 s	0.308 s	0.490 s
Pt. under p. a.	0.65 s	92.3 beat min^{-1}	0.065 s	0.286 s	0.455 s

Healthy subject - systole

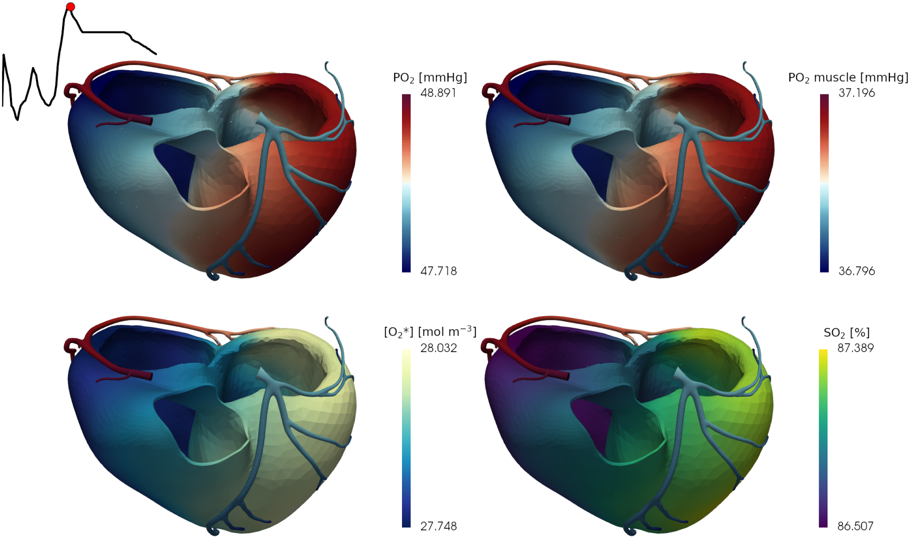
- Subjects without neither coronaries disease nor ischemic myocardial regions



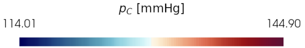
- We observe lower space variability w.r.t. temporal one



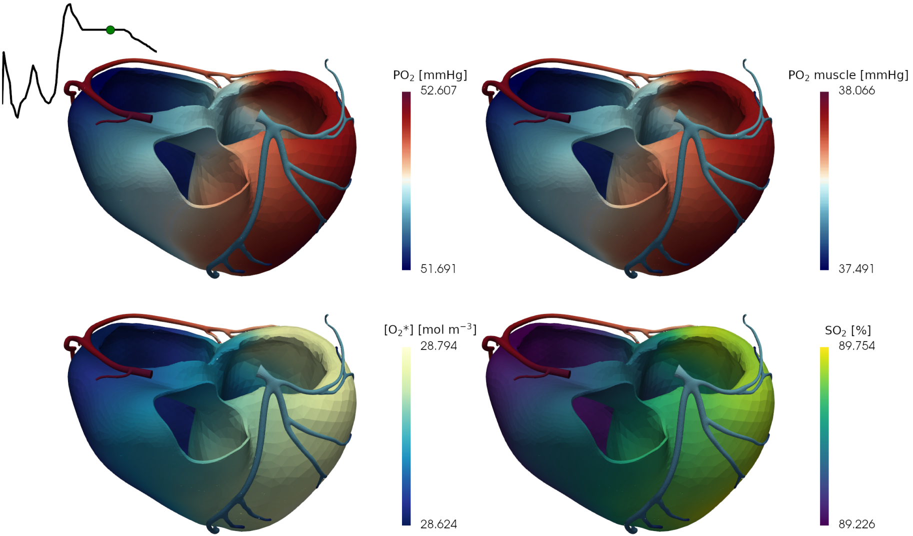
Healthy subject - diastole



- Patterns are similar in each time instant



Healthy subject - plateau



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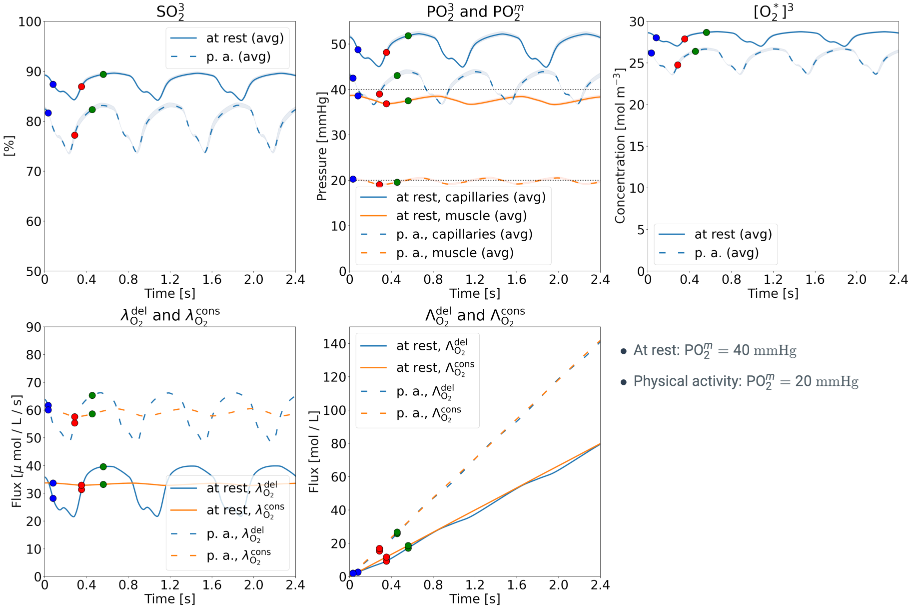
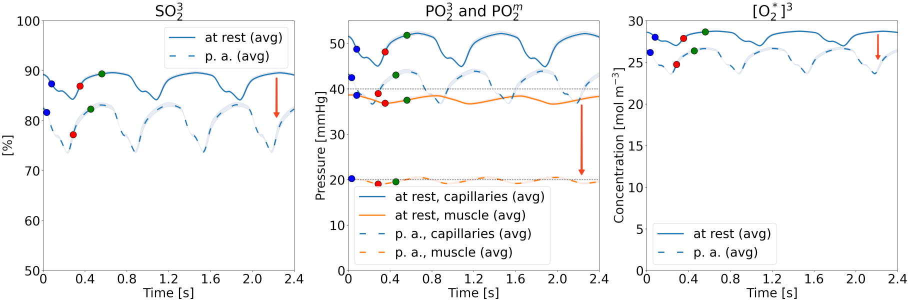
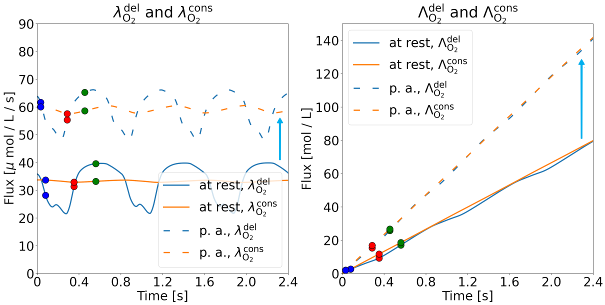
Effects of physical activity



- At rest: $PO_2^m = 40\ \mathrm{mmHg}$
- Physical activity: $PO_2^m = 20\ \mathrm{mmHg}$

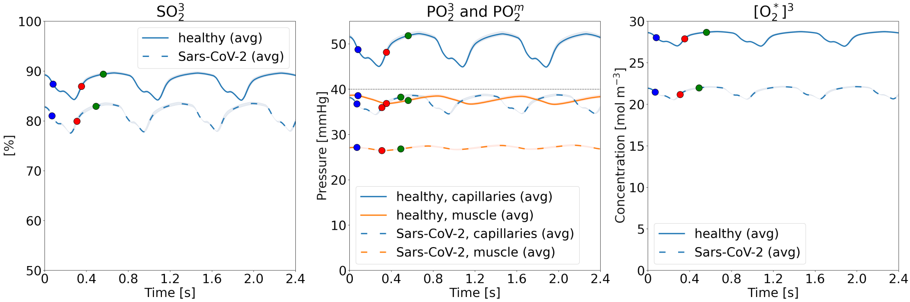
Effects of physical activity

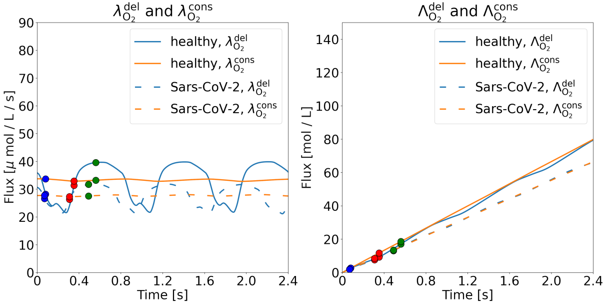




- Increase in $\lambda_{O_2}^{del}$ and $\lambda_{O_2}^{cons}$

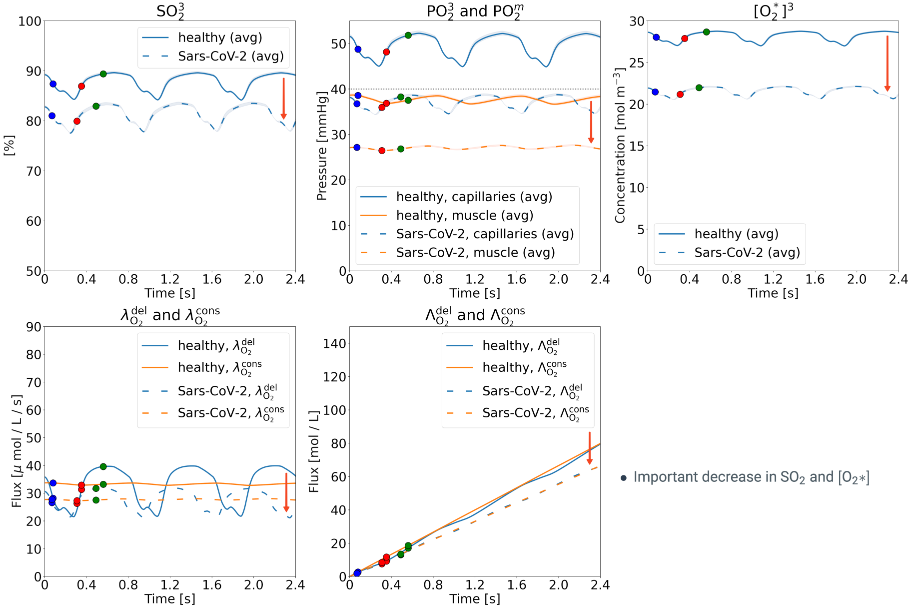
Effects of Sars-CoV-2 infection





- Decrease in PO_2^m w.r.t. physiological value

Effects of Sars-CoV-2 infection



- Important decrease in SO_2 and $[O_2*]$

Conclusions and further developments

Goals achieved

- Biophysical derivation of an innovative multi-physics oxygenation model
- Implementation in life^x, calibration and software verification
- Model’s soundness and clinical relevance confirmed through real-life scenarios simulations

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- Biophysical derivation of an innovative multi-physics oxygenation model
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Further developments

- Study the effect of ischemic regions or coronaries syndromes on oxygenation
- Validate the model through simulations on patient-specific geometries
- Use model output to better study myocardium contraction and improve biophysical fidelity of other models

Essential bibliography

[1] P. C. Africa. *life^x: a flexible, high performance library for the numerical solution of complex finite element problems*. 2022. URL: `https://lifex.gitlab.io/`.

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[3] D. Goldman. “Theoretical Models of Microvascular Oxygen Transport to Tissue”. In: *Microcirculation* 15.8 (2008). PMID: 18608981, pp. 795–811. DOI: `10.1080/10739680801938289`.

[4] R. M. Inciardi et al. “Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy”. In: *European Heart Journal* 41.19 (2020), pp. 1821–1829.

[5] G. Jenkins, C. Kemnitz, and G. J. Tortora. *Anatomy and Physiology: From Science to Life—Second (2nd) Edition*. Wiley, 2009.

[6] A. Quarteroni et al. *Mathematical Modelling of the Human Cardiovascular System: Data, Numerical Approximation, Clinical Applications*. Cambridge Monographs on Applied and Computational Mathematics. Cambridge University Press, 2019.

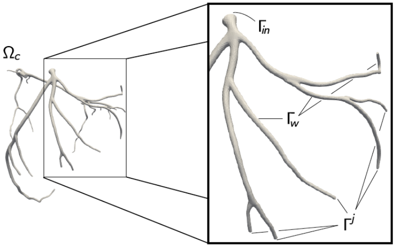
[7] F. Regazzoni. “Oxygen exchange model”. In: *Internal MOX Report, Politecnico di Milano* (2020).

[8] N. Shenoy, R. Luchtel, and P. Gulani. “Considerations for target oxygen saturation in COVID-19 patients: are we under-shooting?” In: *BMC Medicine* 18.1 (2020), pp. 1–6.

[9] Zygote Media Group Inc. *Zygote solid 3D heart generation II developement report*. en. Tech. rep. Zygote Media Group Inc, 2014.

Additional material

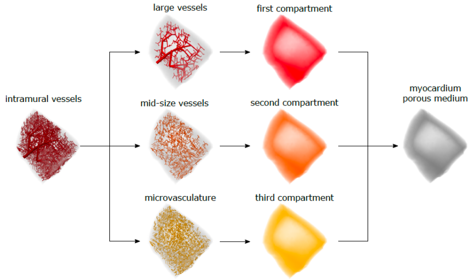
Blood dynamics in epicardial coronary arteries



Navier-Stokes equations

$$
\begin{cases}
\rho\left(\dfrac{\partial \boldsymbol{u}_C}{\partial t} + (\boldsymbol{u}_C \cdot \nabla)\,\boldsymbol{u}_C\right) - \mu_C \nabla \cdot \left(\nabla \boldsymbol{u}_C + (\nabla \boldsymbol{u}_C)^T\right) + \nabla p_C = \boldsymbol{0} & \text{in } \Omega_C, \\
\nabla \cdot \boldsymbol{u}_C = 0 & \text{in } \Omega_C, \\
\boldsymbol{u}_C = \boldsymbol{0} & \text{on } \Gamma_w, \\
\boldsymbol{u}_C = \boldsymbol{u}_{in} & \text{on } \Gamma_{in},
\end{cases}
$$

Blood dynamics in intramural coronary vessels



- $i = 1 \quad \sim 200\ \mu\text{m} \div 1\ \text{mm}$
- $i = 2 \quad \sim 60 \div 200\ \text{mm}$
- $i = 3 \quad \sim 5 \div 60\ \mu\text{m}$

Primal three-compartments Darcy model

$$
\begin{cases}
\boldsymbol{u}_1 + \boldsymbol{K}_1 \nabla p_1 = \boldsymbol{0} & \text{in } \Omega_M \\
\nabla \cdot \boldsymbol{u}_1 = g_1 - \beta_{1,2}\,(p_1 - p_2) & \text{in } \Omega_M \\
\boldsymbol{u}_2 + \boldsymbol{K}_2 \nabla p_2 = \boldsymbol{0} & \text{in } \Omega_M \\
\nabla \cdot \boldsymbol{u}_2 = -\beta_{2,1}\,(p_2 - p_1) - \beta_{2,3}\,(p_2 - p_3) & \text{in } \Omega_M \\
\boldsymbol{u}_3 + \boldsymbol{K}_3 \nabla p_3 = \boldsymbol{0} & \text{in } \Omega_M \\
\nabla \cdot \boldsymbol{u}_3 = -\gamma\,(p_3 - p_v) - \beta_{3,2}\,(p_3 - p_2) & \text{in } \Omega_M \\
\boldsymbol{u}_i \cdot \boldsymbol{n} = 0, \quad i = 1, 2, 3 & \text{on } \partial\Omega_M
\end{cases}
$$

Darcy problem - primal form

$$
\begin{cases}
-\nabla \cdot (\boldsymbol{K}_1 \cdot \nabla p_1) = g_1 - \beta_{1,2}\,(p_1 - p_2) & \text{in } \Omega_M, \\
\boldsymbol{u}_1 \cdot \boldsymbol{n} = 0 & \text{on } \partial\Omega_M, \\
-\nabla \cdot (\boldsymbol{K}_2 \cdot \nabla p_2) = -\beta_{2,1}\,(p_2 - p_1) - \beta_{2,3}\,(p_2 - p_3) & \text{in } \Omega_M, \\
\boldsymbol{u}_2 \cdot \boldsymbol{n} = 0 & \text{on } \partial\Omega_M, \\
-\nabla \cdot (\boldsymbol{K}_3 \cdot \nabla p_3) = -\gamma\,(p_3 - p_v) - \beta_{3,2}\,(p_3 - p_2) & \text{in } \Omega_M, \\
\boldsymbol{u}_3 \cdot \boldsymbol{n} = 0 & \text{on } \partial\Omega_M.
\end{cases}
$$

Parameters

Variable	Measure unit	Value
ρ	$\mathrm{kg\,m^{-3}}$	$1.06 \cdot 10^{-3}$
μ_C	$\mathrm{mmHg\,s}$	$2.63 \cdot 10^{-5}$

Table: List of fluid dynamics parameters.

Variable	Measure unit	Value
γ	$\mathrm{s^{-1}\,mmHg^{-1}}$	0.0133
p_v	mmHg	22.5
$\beta_{1,2}$	$\mathrm{s^{-1}\,mmHg^{-1}}$	$3.5 \cdot 10^{-4}$
$\beta_{2,3}$	$\mathrm{s^{-1}\,mmHg^{-1}}$	$4.8 \cdot 10^{-4}$
$\beta_{1,3}$	$\mathrm{s^{-1}\,mmHg^{-1}}$	0
$\boldsymbol{K}_1$	$\mathrm{m^2\,s^{-1}\,mmHg^{-1}}$	$7.8 \cdot 10^{-3} \cdot \mathbb{I}$
$\boldsymbol{K}_2$	$\mathrm{m^2\,s^{-1}\,mmHg^{-1}}$	$1.1 \cdot 10^{-8} \cdot \mathbb{I}$
$\boldsymbol{K}_3$	$\mathrm{m^2\,s^{-1}\,mmHg^{-1}}$	$0.133 \cdot \mathbb{I}$

Table: List of Darcy problem parameters.

Parameters

Variable	Measure unit	Value
n	—	3.2
PO_2^m	mmHg	40
PO_2^{50}	mmHg	26.7
α	$\mathrm{mmHg\,m^3\,mol^{-1}}$	722.6
$[Hb*]$	$\mathrm{mol\,m^{-3}}$	10
k_-	$\mathrm{s^{-1}}$	100
$\widetilde{P}$	$\mathrm{s^{-1}}$	1
$\widetilde{\xi}_0$	$\mathrm{mmHg\,s^{-1}}$	50
$PO_2^{m,50}$	mmHg	40
ψ_1, ψ_2, ψ_3	—	$3 \cdot 10^{-3}$
μ	$\mathrm{m^2\,s^{-1}}$	0.1

Table: List of oxygenation model parameters.

Mathematical formulation of the coupled problem

Uncoupled problem

$$\boldsymbol{u}_3 = \boldsymbol{0}$$

$$\widehat{\phi}_{2,3}(\boldsymbol{x}, t) \equiv \widehat{\phi}_{3,v}(\boldsymbol{x}, t) = \frac{\Phi_M}{2}\left(1 - \cos\left(\frac{2\pi}{T_{HB}}t\right)\right)$$

where Φ_M $[\mathrm{s}^{-1}]$ is the flux magnitude and T_{HB} $[\mathrm{s}]$ is the heart beat period.

Coupled problem

$$\boldsymbol{u}_3 = -\boldsymbol{K}_3 \nabla p_3$$

$$\widehat{\phi}_{2,3} = \beta_{2,3}(p_3 - p_2)$$

$$\widehat{\phi}_{3,v} = \gamma(p_3 - p_v)$$

where $\boldsymbol{K}_3$ $[\mathrm{m}^2\,\mathrm{s}^{-1}\,\mathrm{mmHg}^{-1}]$ is the permeability tensor of the third compartment, $\beta_{2,3}$ and γ $[\mathrm{mmHg}^{-1}\,\mathrm{s}^{-1}]$ are the inter-compartment pressure-coupling coefficients and p_v $[\mathrm{mmHg}]$ is the blood pressure in venous system.

Multi-physics three-compartments oxygenation model

$$
\begin{cases}
\rho\left(\dfrac{\partial \boldsymbol{u}_C}{\partial t}+(\boldsymbol{u}_C\cdot\nabla)\,\boldsymbol{u}_C\right)-\mu_C\nabla\cdot\left(\nabla\boldsymbol{u}_C+(\nabla\boldsymbol{u}_C)^T\right)+\nabla p_C=\boldsymbol{0} \text{ in } \Omega_C\\
\nabla\cdot\boldsymbol{u}_C=0 \text{ in } \Omega_C\\
p_C-\mu_C\left(\nabla\boldsymbol{u}_C+(\nabla\boldsymbol{u}_C)^T\right)\boldsymbol{n}\cdot\boldsymbol{n}-\dfrac{1}{\alpha^j}\displaystyle\int_{\Gamma^j}\boldsymbol{u}_C\cdot\boldsymbol{n}\,d\gamma=\dfrac{1}{\left|\Omega_M^j\right|}\int_{\Omega_M^j}p_1\,d\boldsymbol{x} \text{ on } \Gamma^j\\
\mu_C\left(\nabla\boldsymbol{u}_C+(\nabla\boldsymbol{u}_C)^T\right)\boldsymbol{n}\cdot\boldsymbol{\tau}_i=0,\quad i=1,2 \text{ on } \Gamma^j\\
\boldsymbol{u}_1+\boldsymbol{K}_1\nabla p_1=\boldsymbol{0} \text{ in } \Omega_M\\
\nabla\cdot\boldsymbol{u}_1=\displaystyle\sum_{j=1}^{J}\dfrac{\chi_{\Omega_M^j}}{\left|\Omega_M^j\right|}\int_{\Gamma^j}\boldsymbol{u}_C\cdot\boldsymbol{n}\,d\gamma-\beta_{1,2}\,(p_1-p_2) \text{ in } \Omega_M\\
\boldsymbol{u}_2+\boldsymbol{K}_2\nabla p_2=\boldsymbol{0} \text{ in } \Omega_M\\
\nabla\cdot\boldsymbol{u}_2=-\beta_{2,1}\,(p_2-p_1)-\beta_{2,3}\,(p_2-p_3) \text{ in } \Omega_M\\
\boldsymbol{u}_3+\boldsymbol{K}_3\nabla p_3=\boldsymbol{0} \text{ in } \Omega_M\\
\nabla\cdot\boldsymbol{u}_3=-\gamma\,(p_3-p_v)-\beta_{3,2}\,(p_3-p_2) \text{ in } \Omega_M\\
\boldsymbol{u}_i\cdot\boldsymbol{n}=0,\quad i=1,2,3 \text{ on } \partial\Omega_M\\
\dfrac{\partial}{\partial t}[\mathrm{O}_2*]^3+\psi_3^{-1}\nabla\cdot\left(-\boldsymbol{K}_3[\mathrm{O}_2*]^3\nabla p_3\right)+\mu\Delta[\mathrm{O}_2*]^3=\\
\quad\psi_3^{-1}\beta_{2,3}(p_3-p_2)[\mathrm{O}_2*]^2-\psi_3^{-1}\gamma(p_3-p_v)[\mathrm{O}_2*]^3\\
\quad-\psi_3^{-1}\widetilde{P}\alpha^{-1}\left(g^{-1}([\mathrm{O}_2*]^3)-\mathrm{PO}_2^m\right) \text{ in } \Omega_M\\
\dfrac{\partial}{\partial t}\mathrm{PO}_2^m=\psi_m^{-1}\widetilde{P}(g^{-1}([\mathrm{O}_2*]^3)-\mathrm{PO}_2^m)-\widetilde{\xi}_0\left(1+\dfrac{\mathrm{PO}_2^{m,50}}{\mathrm{PO}_2^m}\right)^{-1} \text{ in } \Omega_M
\end{cases}
$$

Oxygenation weak problem

Find $[O_2*]^3 \in V$ and $PO_2^m \in W$ such that

$$\begin{cases} \displaystyle\int_{\Omega_M} \frac{\partial}{\partial t}[O_2*]^3 v \, d\boldsymbol{x} + \\ \displaystyle - \int_{\Omega_M} \psi_3^{-1}[O_2*]^3 \boldsymbol{u}_3 \cdot \nabla v \, d\boldsymbol{x} \quad - \int_{\Omega_M} \mu \nabla [O_2*]^3 \nabla v \, d\boldsymbol{x} = \int_{\Omega_M} \psi_3^{-1} \widehat{\phi}_{2,3} [O_2*]^2 v \, d\boldsymbol{x} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad - \displaystyle\int_{\Omega_M} \psi_3^{-1} \widehat{\phi}_{3,v} [O_2*]^3 v \, d\boldsymbol{x} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad - \displaystyle\int_{\Omega_M} \psi_3^{-1} \widetilde{P} \alpha^{-1} \left(g^{-1}([O_2*]^3) - PO_2^m \right) v \, d\boldsymbol{x}, \\ \displaystyle\int_{\Omega_M} \frac{\partial}{\partial t} PO_2^m w \, d\boldsymbol{x} = \int_{\Omega_M} \psi_m^{-1} \widetilde{P} (g^{-1}([O_2*]^3) - PO_2^m) w \, d\boldsymbol{x} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad - \displaystyle\int_{\Omega_M} \widetilde{\xi}_0 \left(1 + \frac{PO_2^{m,50}}{PO_2^m} \right)^{-1} w \, d\boldsymbol{x}, \end{cases}$$

for every test functions $v \in V$ and $w \in W$.

Oxygen fluxes approximation

After solving the problem, we want to compute the average oxygen flux delivered and consumed. We denote as $\overline{a}$ the spatial average of the field a (of course, we consider $\overline{a} \equiv a$ in case of 0D model) so we get, for the timestep k, that

$$\lambda_{\mathrm{O}_2}^{\mathrm{del}}(t_k) \approx \widetilde{P}\alpha^{-1}(g^{-1}(\overline{[\mathrm{O}_2*]^3(t_k)}) - \overline{\mathrm{PO}_2^m(t_k)}), \qquad \lambda_{\mathrm{O}_2}^{\mathrm{cons}}(t_k) \approx \psi_m \widetilde{\xi}_0 \alpha^{-1} \left(1 + \frac{\mathrm{PO}_2^{m,50}}{\overline{\mathrm{PO}_2^m(t_k)}}\right)^{-1}.$$

Finally, to compute the total flux, we integrate the average ones using trapezoidal rule, hence we get, for the timestep k, that

$$\Lambda_{\mathrm{O}_2}^{\mathrm{del}}(t_k) \approx \frac{\Delta t}{2} \sum_{i=1}^{k} \left(\lambda_{\mathrm{O}_2}^{\mathrm{del}}(t_{i-1}) + \lambda_{\mathrm{O}_2}^{\mathrm{del}}(t_i)\right), \quad \Lambda_{\mathrm{O}_2}^{\mathrm{cons}}(t_k) \approx \frac{\Delta t}{2} \sum_{i=1}^{k} \left(\lambda_{\mathrm{O}_2}^{\mathrm{cons}}(t_{i-1}) + \lambda_{\mathrm{O}_2}^{\mathrm{cons}}(t_i)\right).$$

Linear algebraic system

The corresponding linear algebraic system to solve at each time step reads

$$\begin{bmatrix} \mathbb{A}^k & \mathbb{O} \\ \mathbb{O} & \mathbb{B} \end{bmatrix} \begin{bmatrix} [\mathrm{O}_{\mathbf{2}}*]^{3,k+1} \\ \mathrm{PO}_{\mathbf{2}}^{m,k+1} \end{bmatrix} = \begin{bmatrix} \boldsymbol{F}^k \\ \boldsymbol{G}^k \end{bmatrix}$$

$$\begin{aligned}
[\mathbb{A}]_{i,j}^k &= \int_{\Omega_M} \frac{1}{\Delta t}\varphi_j\varphi_i \, d\boldsymbol{x} - \int_{\Omega_M} \mu\nabla\varphi_j\nabla\varphi_i \, d\boldsymbol{x} - \int_{\Omega_M} \varphi_j\psi_3^{-1}\boldsymbol{u}_3^k \cdot \nabla\varphi_i \, d\boldsymbol{x} + \int_{\Omega_M} \psi_3^{-1}\widehat{\phi}_{3,4}^k\varphi_j\varphi_i \, d\boldsymbol{x}, \\
[\mathbb{B}]_{i,j} &= \delta_{ij}, \\
[\boldsymbol{F}]_i^k &= \int_{\Omega_M} \frac{[\mathrm{O}_2*]^{3,k}}{\Delta t}\varphi_i \, d\boldsymbol{x} + \int_{\Omega_M} \psi_3^{-1}\widehat{\phi}_{2,3}^k[\mathrm{O}_2*]^{2,k+1}\varphi_i \, d\boldsymbol{x} \\
&\quad - \int_{\Omega_M} \psi_3^{-1}\widetilde{P}\alpha^{-1}\left(g^{-1}\left([\mathrm{O}_2*]^{3,k}\right) - \mathrm{PO}_2^{m,k}\right)\varphi_i \, d\boldsymbol{x}, \\
[\boldsymbol{G}]_i^k &= \int_{\Omega_M} \mathrm{PO}_2^{m,k}\eta_i \, d\boldsymbol{x} + \int_{\Omega_M} \Delta t\psi_m^{-1}\widetilde{P}(g^{-1}([\mathrm{O}_2*]^{3,k}) - \mathrm{PO}_2^{m,k})\eta_i \, d\boldsymbol{x} \\
&\quad - \int_{\Omega_M} \Delta t\widetilde{\xi}_0\left(1 + \frac{\mathrm{PO}_2^{m,50}}{\mathrm{PO}_2^{m,k}}\right)^{-1}\eta_i \, d\boldsymbol{x}.
\end{aligned}$$

Fourth-order Runge-Kutta for 0D model

Neglecting the space dependencies and properly group the unkownks, we get the ODEs system

$$\begin{cases} \dot{\boldsymbol{y}}(t) = \boldsymbol{f}(t, \boldsymbol{y}(t)), \quad t \in [0, T] \\ \boldsymbol{y}(0) = \boldsymbol{y}_0, \end{cases}$$

we can solve with the following Runge-Kutta of order fourth order.

Algorithm Fourth-order Runge-Kutta method

1: **for** $k = 0, \dots, N_{\Delta t} - 1$ **do**

2: Compute at timestep k:

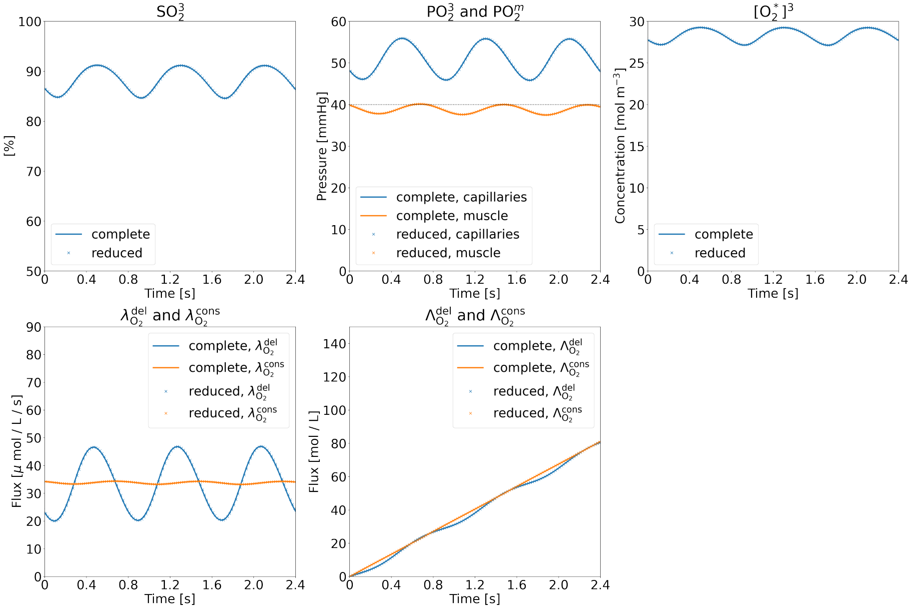
$$\begin{aligned} \boldsymbol{RK}_1 &:= \boldsymbol{f}\left(t_k, \boldsymbol{y}_k\right) \\ \boldsymbol{RK}_2 &:= \boldsymbol{f}\left(t_k + \frac{\Delta t}{2}, \boldsymbol{y}_k + \frac{\Delta t}{2}\boldsymbol{RK}_1\right) \\ \boldsymbol{RK}_3 &:= \boldsymbol{f}\left(t_k + \frac{\Delta t}{2}, \boldsymbol{y}_k + \frac{\Delta t}{2}\boldsymbol{RK}_2\right) \\ \boldsymbol{RK}_4 &:= \boldsymbol{f}\left(t_{k+1}, \boldsymbol{y}_k + \Delta t \boldsymbol{RK}_3\right) \end{aligned}$$

3: Compute at timestep k:

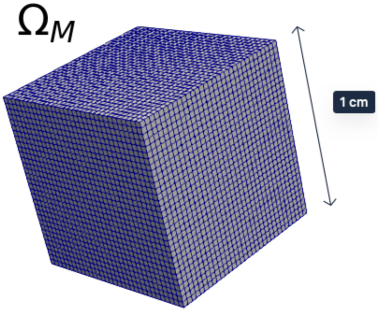
$$\boldsymbol{y}_{k+1} = \boldsymbol{y}_k + \frac{\Delta t}{6}\left(\boldsymbol{RK}_1 + 2\boldsymbol{RK}_2 + 2\boldsymbol{RK}_3 + \boldsymbol{RK}_4\right)$$

4: **end for**

Comparison between complete and reduced 0D models



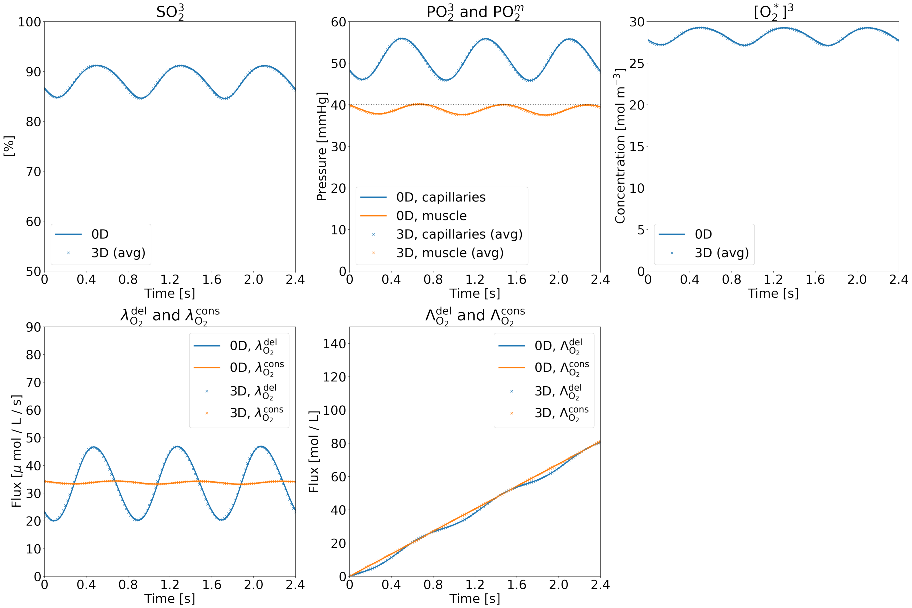
Idealized myocardium geometry

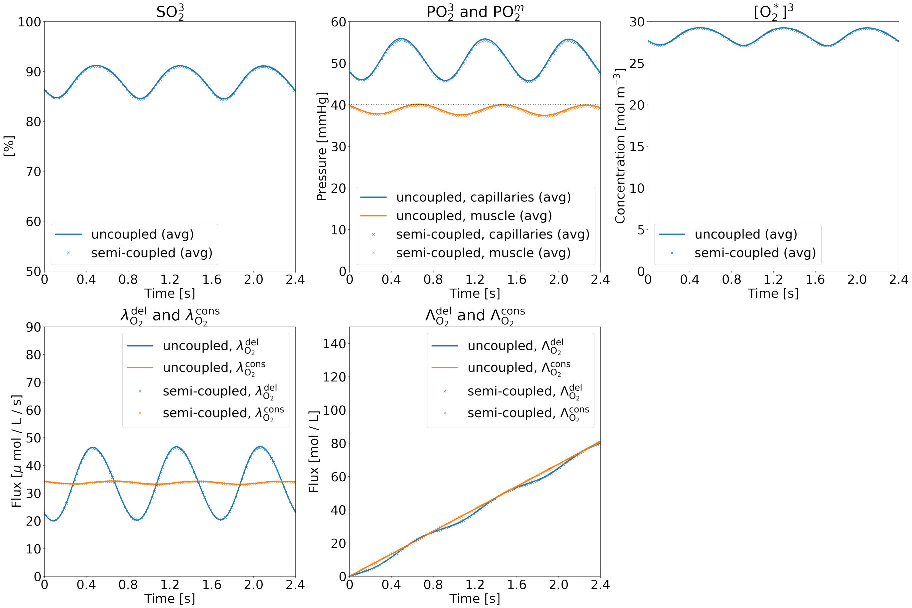


- $\boldsymbol{u}_3 = \boldsymbol{0}$
- $\widehat{\phi}_{2,3}(\boldsymbol{x}, t) \equiv \widehat{\phi}_{3,m}(\boldsymbol{x}, t) = \frac{\Phi_M}{2}\left(1 - \cos\left(\frac{2\pi}{T_{HB}} t\right)\right)$

Variable	Measure unit	Value
Φ_M	s^{-1}	0.021
T_{HB}	s	0.8

Comparison between reduced 3D and 0D model



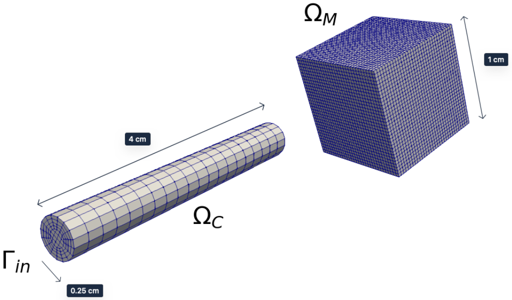


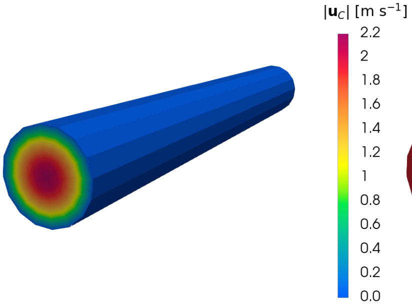
SO_2^3
[%]
uncoupled (avg)
semi-coupled (avg)
Time [s]
PO_2^3 and PO_2^m
Pressure [mmHg]
uncoupled, capillaries (avg)
uncoupled, muscle (avg)
semi-coupled, capillaries (avg)
semi-coupled, muscle (avg)
$[O_2^*]^3$
Concentration [mol m^{-3}]
$\lambda_{O_2}^{del}$ and $\lambda_{O_2}^{cons}$
Flux [μ mol / L / s]
uncoupled, $\lambda_{O_2}^{del}$
uncoupled, $\lambda_{O_2}^{cons}$
semi-coupled, $\lambda_{O_2}^{del}$
semi-coupled, $\lambda_{O_2}^{cons}$
$\Lambda_{O_2}^{del}$ and $\Lambda_{O_2}^{cons}$
Flux [mol / L]
uncoupled, $\Lambda_{O_2}^{del}$
uncoupled, $\Lambda_{O_2}^{cons}$
semi-coupled, $\Lambda_{O_2}^{del}$
semi-coupled, $\Lambda_{O_2}^{cons}$

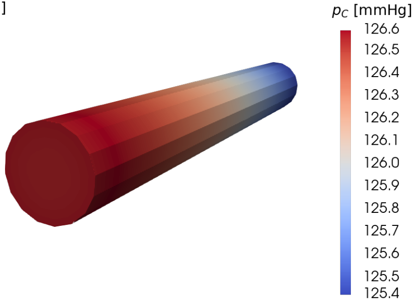
Idealized geometries

$$\boldsymbol{u}_{in}(r,\theta,0,t) \equiv |\Omega_M| \begin{bmatrix} 0 \\ 0 \\ 1-\left(\frac{r}{r_C}\right)^2 \end{bmatrix} \Phi(t),$$

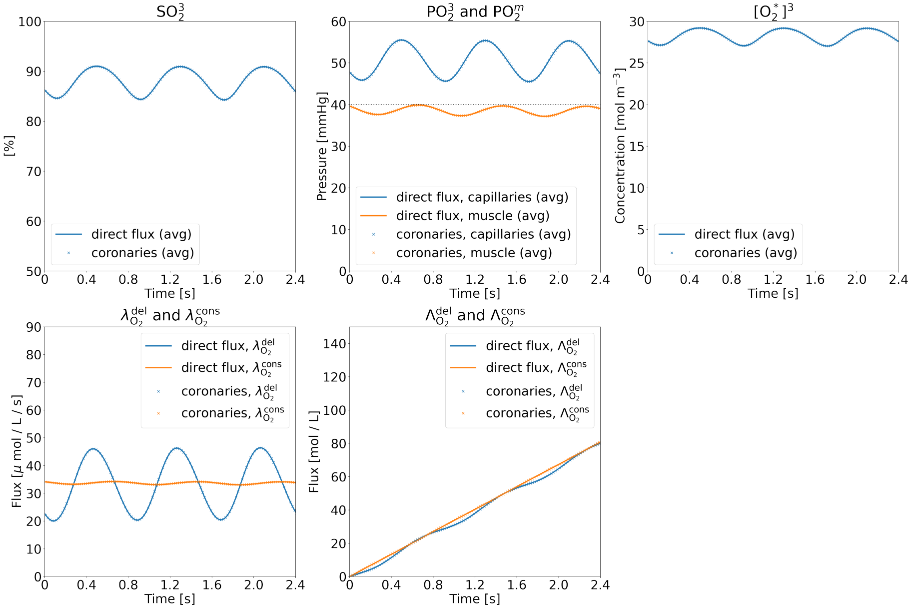
$$r \in [-r_C, r_C]\,,\ \theta \in [0, 2\pi]$$



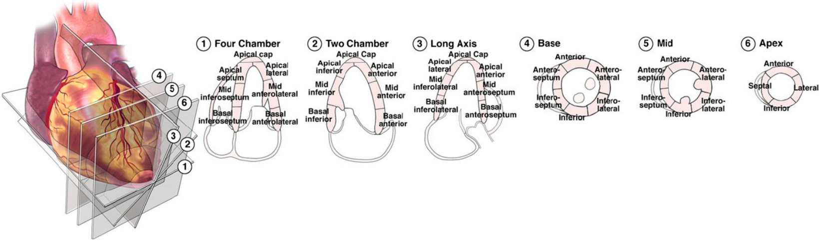


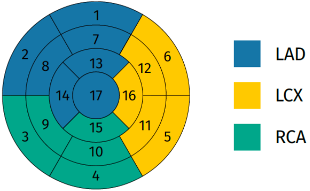


Comparison between coupled and perfusion-coupled model

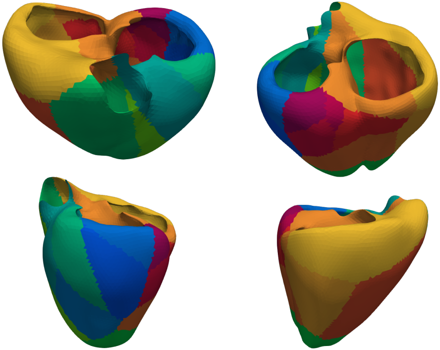


Perfusion regions



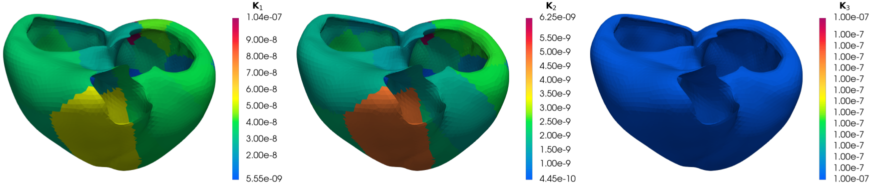


1.	basal anterior	7.	mid anterior	13.	apical anterior
2.	basal anteroseptal	8.	mid anteroseptal	14.	apical septal
3.	basal inferoseptal	9.	mid inferoseptal	15.	apical inferior
4.	basal inferior	10.	mid inferior	16.	apical lateral
5.	basal inferolateral	11.	mid inferolateral	17.	apex
6.	basal anterolateral	12.	mid anterolateral		

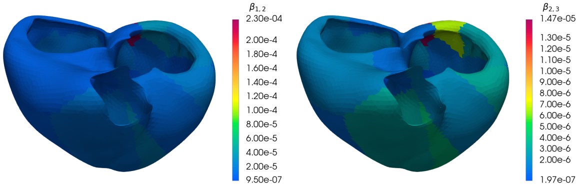


Parameters

- $K_i, \ i = 1, 2, 3$



- $\beta_{i,j}, \ i, j = 1, 2, 3$



Coronary blood flow (CBF)

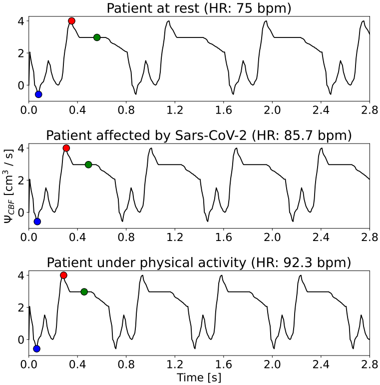
The averaged flux of blood flowing from the compartment $i-1$ to i inside a tissue myocardium volume Ω_M, and during a heart cycle $[0, T]$ is the average CBF and can be computed as

$$\overline{\Psi}_{\mathrm{CBF}} := \frac{1}{T|\Omega_M|}\int_0^T \int_{\Omega_M} \widehat{\phi}_{i-1,1}\, d\boldsymbol{x}\, dt$$

Its typical value is nearly $0.8\ \mathrm{mL\,min^{-1}\,g^{-1}}$. At the inlet sections $\Gamma_{in,k},\ k=l,r$ of the epicardial left ($k=l$) and right ($k=r$) vessel, we prescribe the flow rate condition

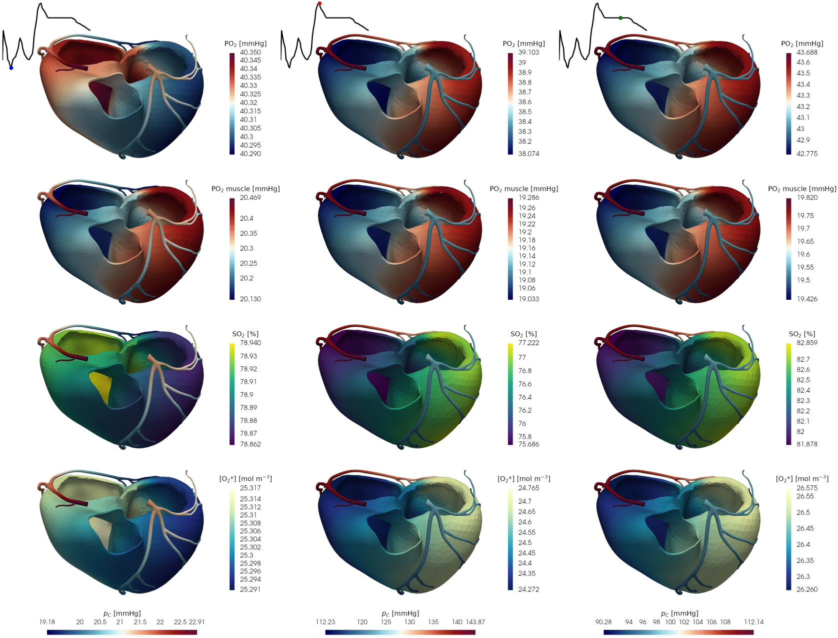
$$\int_{\Gamma_{in,k}} \boldsymbol{u}_C \cdot \boldsymbol{n} d\gamma = \Psi_{\mathrm{CBF}k},\ k=l,r$$

- left: $\Psi_{\mathrm{CBF}l} = 0.57\Psi_{\mathrm{CBF}}$
- right: $\Psi_{\mathrm{CBF}r} = 0.43\Psi_{\mathrm{CBF}}$
- $\overline{\Psi}_{\mathrm{CBF}} = 0.695\ \mathrm{mL\,min^{-1}\,g^{-1}}$

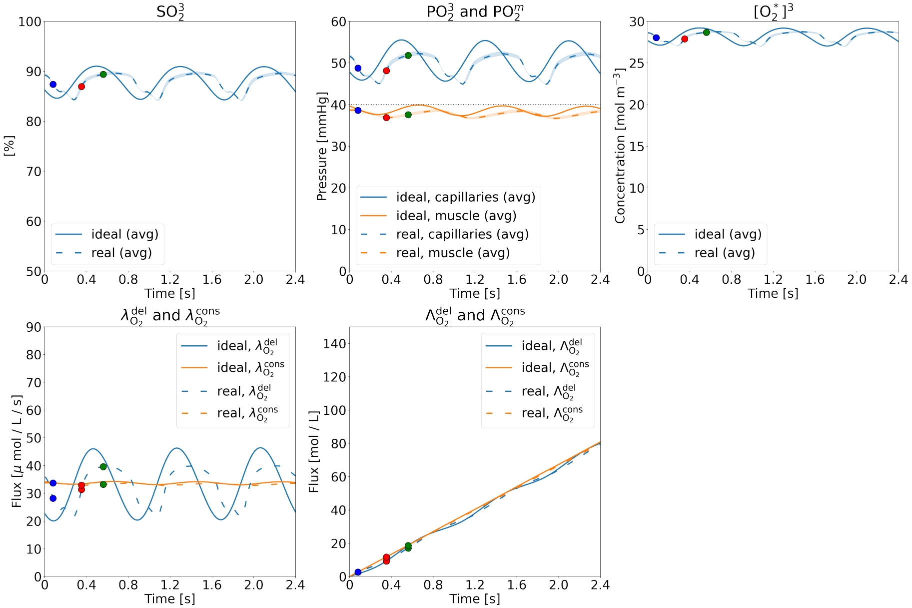


Scenario	Period	HR	Color: Blue	Red	Green
Pt. at rest	$0.8\ \mathrm{s}$	$75\ \mathrm{beat\,min^{-1}}$	$0.08\ \mathrm{s}$	$0.352\ \mathrm{s}$	$0.560\ \mathrm{s}$
Pt. with SARS-CoV-2	$0.7\ \mathrm{s}$	$85.7\ \mathrm{beat\,min^{-1}}$	$0.070\ \mathrm{s}$	$0.308\ \mathrm{s}$	$0.490\ \mathrm{s}$
Pt. under p. a.	$0.65\ \mathrm{s}$	$92.3\ \mathrm{beat\,min^{-1}}$	$0.065\ \mathrm{s}$	$0.286\ \mathrm{s}$	$0.455\ \mathrm{s}$

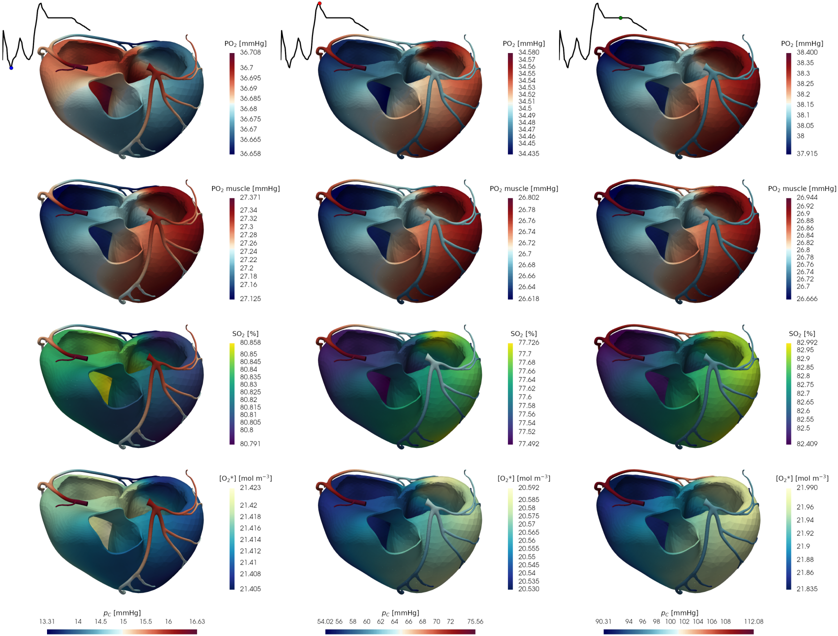
Healthy subject under physical activity



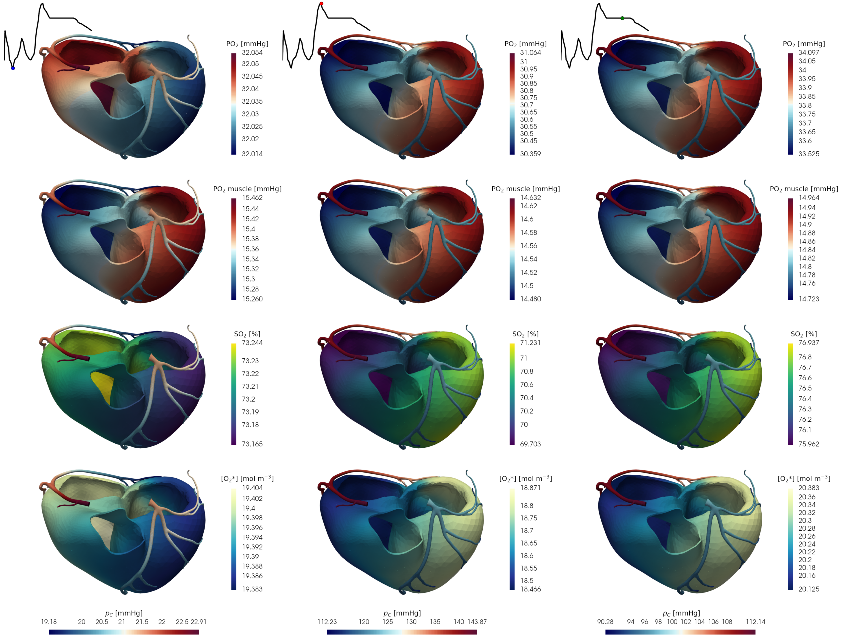
Comparison between real and idealized geometry



Patient with Sars-CoV-2 infection



Patient with SARS-CoV-2 infection and under p. a.



Effects of physical activity and SARS-CoV-2 disease